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Interpatient variability in bioavailability of the intravenous formulation of topotecan given orally to children with recurrent solid tumors

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Abstract *Purpose*: Evaluation of inter- and intrapatient variability of topotecan oral bioavailability and disposition was performed in children with malignant solid tumors. *Patients and methods*: Topotecan i.v. formulation was given orally on schedules of daily for 21 consecutive days (d × 21) or daily for 5 days per week for 3 weeks [(d × 5)3], in both cases repeated every 28 days. Topotecan doses of 0.8 and 1.1 mg/m^2 per day were evaluated on both schedules. Serial plasma samples were obtained after oral and i.v. administration of topotecan at the beginning and end of the first course of therapy. Topotecan lactone and total concentrations were measured by a high-performance liquid chromatography (HPLC) assay, and a one-or two-compartment model was fit to the plasma concentration-time data after oral or i.v. administration, respectively. Topotecan oral bioavailability (F) was calculated as the ratio of the AUC determined after oral treatment (AUC_{po}) divided by the AUC calculated after i.v. administration. *Results*: Pharmacokinetics studies were performed on 15 and 11 patients receiving 0.8 and 1.1 mg/m^2 per day, respectively. After oral administration the topotecan lactone AUC_{po} and F determined for 0.8 and 1.1 mg/m^2 per day were 13.6 ± 5.8 and 25.1 ± 12.9 ng ml^{-1} h and 0.34 ± 0.14 and 0.34 ± 0.16, respectively. The within-patient variance for AUC_{po} and F was much smaller than the between-patient variance. The ratio of topotecan lactone to total concentration was consistently higher after oral as compared with i.v. administration. *Conclusions*: Large interpatient variability was noted in topotecan pharmacokinetics, whereas intrapatient variability was relatively small. Further studies of oral topotecan are warranted to evaluate the tolerance of shorter courses and to define further the interpatient variability.

Key words Topotecan · Oral bioavailability · Pediatric solid tumors

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Introduction

Topotecan, a semisynthetic water-soluble analog of camptothecin, has shown promising activity in preclinical and clinical studies in children with cancer [1, 2]. In early clinical trials, topotecan has been given i.v. as an infusion over periods ranging from 30 min to 21 days [3, 4] and orally by once- or twice-daily dosing [5, 6]. Preclinical data from our institution and others suggest that protracted administration of low-dose topotecan achieves better antitumor activity than less frequent administration of higher doses [7–10]. Oral administration of topotecan would mimic the protracted schedule used successfully in preclinical studies, and it would

maximize patient convenience and minimize use of clinical resources.

Oral absorption of other anticancer drugs has been characterized by extensive inter- and intrapatient variability in oral bioavailability [11, 12]. Prior studies have evaluated oral topotecan given as once- and twice-daily doses to adults with solid tumors [5, 6]. Schellens and colleagues [5] reported topotecan bioavailability of 0.30 ± 0.08 (range 0.21 to 0.45) in 12 adults with solid tumors. However, they did not report intrapatient variability in topotecan bioavailability. Creemers and colleagues [6] gave oral topotecan to 14 adults and measured topotecan plasma concentrations on days 1 and 8. Contrary to the results of Schellens et al. [5], these investigators found a small but detectable accumulation of topotecan on day 8. Thus, in the present study we evaluated the interpatient variability in topotecan oral bioavailability and pharmacokinetics in children with solid tumors receiving the i.v. formulation of topotecan orally. Moreover, we evaluated the intrapatient variability in topotecan bioavailability and disposition during a single course of therapy.

Patients and methods

Eligibility

Patients less than 21 years of age who had histologically documented solid tumors refractory to conventional therapy or for whom no effective therapy existed were candidates for this pharmacokinetics study. Other eligibility criteria included a life expectancy of at least 4 weeks, recovery from toxic effects of previous chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients also had adequate hematological, hepatic, and renal function. Exclusion criteria included persistent nausea and vomiting, radiation enteritis, short-gut syndrome, or any other gastrointestinal or esophageal dysfunction that would interfere with swallowing or absorption. The St. Jude Children's Research Hospital Institutional Review Board approved the study, and informed, written consent was obtained from the patient, parent, or guardian.

Drug formulation and administration

The NCI Division of Cancer Treatment supplied topotecan AC as the lyophilized light-yellow powder in vials containing 5 mg of topotecan base, 60 mg mannitol, and 25.5 mg tartaric acid. The pH was adjusted to 3.0. For oral administration the i.v. formulation of topotecan was reconstituted with 2 ml of bacteriostatic water for injection, USP, and the dose was drawn up into individual plastic oral syringes. Immediately prior to ingestion by the patient the topotecan dose was mixed in fruit juice (i.e., apple, orange, or grape juice) as a vehicle to ease oral administration. The choice of fruit juice did not affect topotecan oral bioavailability since the drug was in the juice only for seconds prior to ingestion by the patient. For i.v. administration, topotecan was reconstituted with 2 ml of sterile water for injection, USP, and further dilutions were made in 5% dextrose in water; i.v. topotecan was infused over 30 min.

Topotecan doses and schedules

The initial topotecan schedule involved oral administration once a day for 21 consecutive days, with courses being repeated every 4 weeks {[(d × 21)]4}. A second schedule was evaluated in which topotecan was given orally daily for 5 days per week for 3 weeks, with courses being repeated every 4 weeks {[(d × 5)3]4}. Thus, topotecan was given on 21 of 28 days on the first schedule versus 15 of 28 days on the second schedule. Topotecan dose levels of 0.8 and 1.1 mg/m^2 per day were evaluated on each schedule.

Sample collection, preparation, and analysis by HPLC

On the first schedule of topotecan {[(d × 21)]4}, plasma samples for pharmacokinetic analysis were obtained on days 1, 2, 20, and 21 of the first course. Patients were randomized to receive their day-1 topotecan dose either orally or as a 30-min i.v. infusion, and the day-2 dose was given by the alternative route. Topotecan doses on days 20 and 21 were given orally and i.v., respectively. All doses for pharmacokinetics studies were given at 9:00 a.m., and patients fasted for 2 h before and 1 h after oral administration. Plasma samples were obtained before and at 0.5, 1, 3, 6, and 24 h after i.v. administration and before and at 0.25, 0.5, 1.5, 3, 4, 6, and 8 h after oral administration. On the second schedule of topotecan {[(d × 5)3]4}, identical methodology was used with the exception of the topotecan doses on day 18 and 19, which were given by the oral and i.v. routes, respectively.

For each time point, 3 ml of blood was collected from a site contralateral to the topotecan infusion after i.v. administration and was placed in a heparinized tube. Immediately after collection (e.g., within 2 min) the blood sample was centrifuged in a microfuge for 2 min at 7200 *g*. Plasma was separated, and 200 µl of plasma was added to 800 µl of cold (−30 °C) methanol. The methanolic mixture was vortexed for 10 s and then centrifuged for 2 min at 7200 *g*. The supernatant was decanted into a screw-top tube and stored at −70 °C until analyzed by high-performance liquid chromatography (HPLC). Topotecan lactone and total (sum of lactone and hydroxy acid) plasma samples were measured by an isocratic HPLC assay with fluorescence detection using a previously published method [13–16]. Topotecan was detected using a fluorescence detector (Shimadzu RF535, Columbia, Md.) with excitation at 370 nm and emission at 520 nm. Calibration curves were constructed using single-donor human plasma. The minimally detectable topotecan lactone and total plasma concentration was 0.25 ng/ml.

Pharmacokinetic analysis

A one- or two-compartment model was fit using maximum-likelihood and Bayesian estimation to topotecan lactone and total plasma concentrations after oral and i.v. administration, respectively (ADAPT II) [17]. For oral administration the model parameters estimated included the volume of the central compartment (V_c), the absorption rate constant (k_a), and the elimination rate constant (k_e). For i.v. administration the model parameters estimated included the volume of the central compartment (V_c), the elimination rate constant (k_e), and the intercompartment rate constants (k_{cp}, k_{pc}). Using standard equations, we calculated the systemic clearance (CL) and volume of distribution at steady state (Vd_{ss}) from parameter estimates [18].

The area under the plasma concentration-time curve from zero to infinity ($AUC_{0\rightarrow\infty}$) was calculated using the log-linear trapezoidal method [18]. Topotecan oral bioavailability (F) was calculated as the ratio of the AUC calculated after oral administration divided by the AUC determined after i.v. administration. The ratio of topotecan lactone to total concentration was calculated for each measured plasma sample, and for statistical analysis these values were grouped at intervals of 0–3, 3.1–6, and >6 h after oral and i.v. administration.

Statistical analysis

Topotecan pharmacokinetic parameters are reported as mean values ± standard deviations and median values (ranges). The analysis of variance model for repeated measures [19] was utilized to

assess if topotecan pharmacokinetic parameters CL and F changed between the beginning and the end of a course of therapy. We also used this approach to evaluate if these parameters changed between schedules (21-day versus 15-day) and between dose levels (0.8 and 1.1 mg/m^2). The lactone-to-total-concentration ratios in multiple samples were analyzed using a repeated-measures model [20]. The distribution of CL based on data from both schedules and both doses was examined using the quantile-quantile plot.

Results

Patients' characteristics

From December 1994 to March 1996, 26 patients were enrolled in this pharmacokinetics study of oral topotecan in children with refractory solid tumors. The patients' characteristics are listed in Table 1. Although this was not mandated prior to the beginning of the study, none of the patients received drugs known to alter drug absorption on the day of the oral topotecan pharmacokinetics study. In all, 12 patients were treated on schedule 1 and 14, on schedule 2. All patients tolerated administration of the i.v. topotecan formulation orally without significant nausea or vomiting. Each patient was scheduled to have four pharmacokinetics studies, one after the i.v. and the oral dose at the beginning and the end of the first course. Pharmacokinetics studies were inevaluable due to the following reasons: failure to obtain venous access (4), treatment discontinued due to thrombocytopenia (9), and HPLC problems (1).

At the time of the first pharmacokinetics study, all patients had normal age-adjusted serum creatinine (median 0.7 mg/dl, range 0.3–1.1 mg/dl), total bilirubin (median 0.5 mg/dl, range 0.3–1.3 mg/dl), and serum albumin (median 3.9 g/dl, range 3.3–4.5 g/dl) levels.

Pharmacokinetics

Representative topotecan lactone and total plasma concentrations measured after oral and i.v. administration are presented in Figs. 1 and 2, respectively. We studied 45 i.v. topotecan courses, and all were well fit to a two-compartment model ($r^2 > 0.96$) except for 1 ($r^2 = 0.91$). We studied 51 oral topotecan courses, and a one-compartment model with oral absorption was fit to the concentration-time data. As one might expect, the fits from the oral data were more variable, but 75% of

Table 1 Patients' characteristics[a]

Pt #	Schedule	Diagnosis	Sex	Age (years)	BSA (m^2)
0.8 mg/m^2/day:					
1	1	RMS	M	4.5	0.71
2	1	MB	M	5.9	0.74
3	1	PNET	M	21.1	1.85
4	1	Glioma	M	2.8	0.60
5	1	NB	M	6.4	0.90
6	1	OS	M	16.7	1.72
7	2	MB	M	11.0	0.92
8	2	NB	M	2.1	0.63
9	2	Colon	M	14.1	1.55
10	2	ES	M	16.5	1.75
11	2	OS	F	18.9	1.85
12	2	Epend	M	4.5	0.75
13	2	NB	F	5.5	0.80
14	2	RMS	F	14.9	1.39
15	2	NET	F	1.8	0.42
			11 M, 4 F	Median 6.4 Range 1.7–21.1	
1.1 mg/m^2/day:					
1	1	Epend	F	10.3	0.88
2	1	NB	M	12.3	1.23
3	1	NB	M	4.4	0.70
4	1	RMS	M	16.6	1.42
5	1	NB	F	12.4	1.22
6	1	ES	M	12.4	0.97
7	2	OS	M	14.2	1.32
8	2	MB	F	12.3	1.28
9	2	Adrenal Cort	F	19.4	1.76
10	2	Astrocytoma	F	15.1	2.30
11	2	OS	F	17.1	1.26
			5 M, 6 F	Median 12.4 Range 4.4–19.4	

[a] Patients are grouped by dose (0.8 or 1.1 mg/m^2) and schedule {schedule 1 [(d × 21)]4, schedule 2 [(d × 5)3]4} (*RMS* rhabdomyosarcoma, *MB* medulloblastoma, *PNET* primitive neuroectodermal tumor, *NB* neuroblastoma, *OS* osteosarcoma, *Colon* colon adenocarcinoma, *ES* Ewing's sarcoma, *Epend* ependymoma, *NET* neuroectodermal tumor, *Adrenal Cort* adrenal cortical carcinoma)

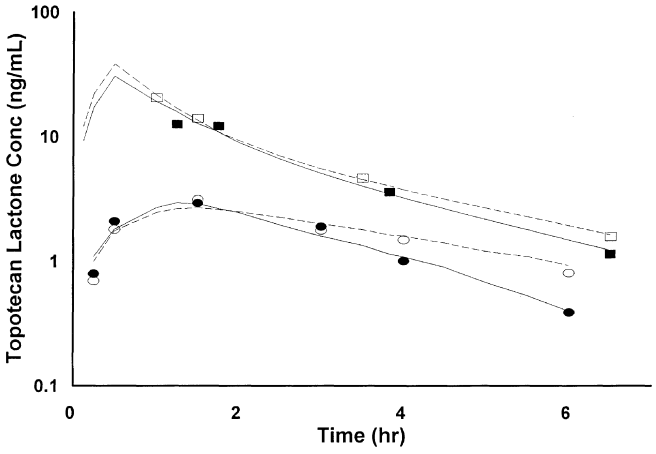

Fig. 1 Topotecan lactone concentration-time plots generated after a 0.8-mg/m^2 dose had been given i.v. and orally to a representative patient on days 1 and 2 and days 18 and 19. Individual data points and the best-fit line of the data are represented for topotecan lactone on day 1 (—, ■) and day 19 (---, □) after i.v. administration and on day 2 (—, ●) and day 18 (---, ○) after oral administration

the courses had r^2 values of >0.9. Even the 13 oral studies with r^2 values of <0.9 upon visual inspection were good fits. Pharmacokinetic parameters determined for topotecan lactone and total concentration are listed in Tables 2 and 3, respectively.

After oral administration, topotecan peak lactone and total plasma concentrations occurred from 0.75 to 2 h. The absorption half-life of topotecan lactone was 0.78 ± 0.54 h. The percent AUC_{po} extrapolated after the last measured time point was 14.9 ± 8.3 (range 2.6–28.5).

Results of the analysis of variance for repeated measures showed that the topotecan lactone CL and F did not differ significantly between the two doses (0.8 and 1.1 mg/m^2, $P = 0.49$ for CL, $P = 0.43$ for F), between the 15-day and the 21-day schedules ($P = 0.99$ for CL, $P = 0.43$ for F), or from the beginning of the course to the end of the course ($P = 0.26$ for CL, $P = 0.80$ for F; see Figs. 3, 4). The within-patient variance of 12.2 for CL and 0.00112 for F was much smaller than the between-patient variance of 101.8 for CL and 0.0327 for F. The results of the analysis of the topotecan total concentration were similar and showed no difference between dose levels, between dosing schedules, or from the beginning of the course to the end of the course (all $P > 0.10$). As in the case of topotecan lactone, the within-patient variance of 11.1 for CL and 0.0066 for F was smaller than the between-patient variance of 46.3 for CL and 0.015 for F.

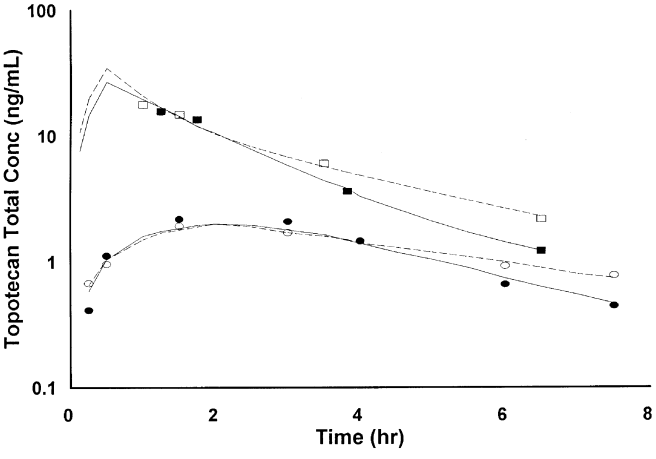

Fig. 2 Topotecan total concentration-time plots generated after a 0.8-mg/m^2 dose had been given i.v. and orally to a representative patient on days 1 and 2 and days 18 and 19. Individual data points and the best-fit line of the data are represented for total topotecan on day 1 (—, ■) and day 19 (---, □) after i.v. administration and on day 2 (—, ●) and day 18 (---, ○) after oral administration

The ratio of topotecan lactone to total concentration (L/T) for i.v. dosing was similar at each of the intervals examined (e.g., 0–3, 3–6, and 6 + h) and at the beginning and the end of the course of therapy. However, the L/T ratio measured after oral dosing changed with time. At the beginning of the course the ratio decreased to the lowest level at 4.5 h after the dose and then slightly increased. A regression analysis suggests both the significant cubic relationships between the L/T ratio and the sampling time after oral administration. The L/T ratio at 0–3 h (0.81 ± 0.032) was significantly higher than that at 3–6 h (0.61 ± 0.032) and that at over 6 h (0.68 ± 0.033; $P = 0.0001$), whereas the L/T ratio at 3–6 h was moderately lower than that at >6 h ($P = 0.0336$).

At the end of the course the L/T ratio dropped initially and then leveled off. The regression analysis with cubic term suggested that the L/T ratio was significantly linearly related only to the time of sampling ($P = 0.01$) after oral administration. The L/T ratio at 0–3 h (0.81 ± 0.037) was significantly higher than that at 3–6 h (0.68 ± 0.034) and that at >6 h (0.69 ± 0.036; $P = 0.0032$), whereas the L/T ratio at 3–6 h did not differ significantly from that at >6 h ($P = 0.96$).

A comparison of L/T ratios was made between oral and i.v. dosing at the intervals of 0–3, 3–6, and >6 h using an analysis of variance model. At the beginning of the course the L/T ratio was higher after oral administration than after i.v. infusion (0.82 ± 0.04 versus 0.57 ± 0.04, 0.63 ± 0.04 versus 0.54 ± 0.04, and 0.68 ± 0.04 versus 0.57 ± 0.04 at 0–3, 3–6, and >6 h, respectively; $P = 0.0001$). At the end of the course the L/T ratio recorded for oral administration was significantly higher than that noted for i.v. administration at each interval (0.80 ± 0.038 versus 0.69 ± 0.036, 0.68 ± 0.035 versus 0.57 ± 0.047, and 0.69 ± 0.038 versus 0.59 ± 0.047 at 0–3, 3–6, and >6 h, respectively; $P = 0.0001$).

Discussion

Although prior studies in adults have evaluated topotecan bioavailability and disposition after oral administration [5, 6], this is the first study evaluating the

Table 2 Summary of topotecan lactone pharmacokinetic parameters[a]

	0.8 mg/m^2/dose			1.1 mg/m^2/dose		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
Intravenous dose:						
V_c (l/m^2)	22.8 ± 14.2	16.6	5.5–68.3	22.0 ± 6.9	20.5	7.5–33.5
K_e (h^{-1})	1.29 ± 0.74	1.14	0.31–3.07	0.85 ± 0.22	0.92	0.52–1.22
$t_{1/2\beta}$ (h)	3.6 ± 2.8	2.2	1.7–12.0	3.5 ± 1.6	2.5	1.1–6.4
CL (l h^{-1}m^{-2})	21.9 ± 7.2	21.6	10.6–36.3	17.5 ± 5.3	17.8	9.2–29.3
Oral dose:						
K_a (h^{-1})	2.3 ± 2.3	1.6	0.3–11.4	2.9 ± 3.7	2.2	0.2–15.1
AUC_{po} (ng ml^{-1} h)	13.6 ± 5.8	13.0	3.8–27.7	25.1 ± 12.9	20.4	7.5–46.9
F	0.34 ± 0.16	0.26	0.14–0.72	0.33 ± 0.16	0.25	0.14–0.7

[a] Parameters were determined after i.v. and oral topotecan doses of 0.8 and 1.1 mg/m^2

Table 3 Summary of topotecan total pharmacokinetic parameters[a]

	0.8 mg/m^2/dose			1.1 mg/m^2/dose		
	Mean ± SD	Median	Range	Mean ± SD	Median	Range
Intravenous dose:						
V_c (l/m^2)	22.1 ± 13.4	17.8	6.8–63.3	17.7 ± 5.4	17.5	5.4–30.0
K_e (h^{-1})	0.8 ± 0.5	0.7	0.3–2.2	0.7 ± 0.3	0.6	0.3–1.1
$t_{1/2\beta}$ (h)	3.1 ± 1.9	2.4	1.5–6.8	2.8 ± 0.5	2.7	0.5–3.9
CL (l h^{-1} m^{-2})	15.1 ± 5.3	13.7	5.3–28.6	11.1 ± 4.1	9.8	4.1–22.2
Oral dose:						
AUC_{po} (ng ml^{-1} h)	15.7 ± 7.1	15.7	5.5–30.1	30.4 ± 13.0	30.5	9.0–57.9
F	0.3 ± 0.1	0.2	0.1–0.5	0.3 ± 0.1	0.3	0.1–0.4

[a] Parameters were determined after i.v. and oral topotecan doses of 0.8 and 1.1 mg/m^2

change in oral topotecan bioavailability and disposition over 2 or 3 weeks of treatment. Results of our compartmental pharmacokinetic analysis of oral topotecan showed a wide interpatient variability in the absorption rate (K_a). In addition, we observed in this study a relatively large interpatient variability in topotecan disposition (e.g., 3-fold variability in topotecan lactone systemic clearance and 6-fold variability in oral bioavailability), whereas intrapatient variability within a single course of therapy was relatively small.

Topotecan disposition after oral administration in our study was consistent with that obtained in prior studies [5, 6, 21–23]. Schellens and colleagues [5] reported an F for topotecan lactone of 0.30 ± 0.08 after a

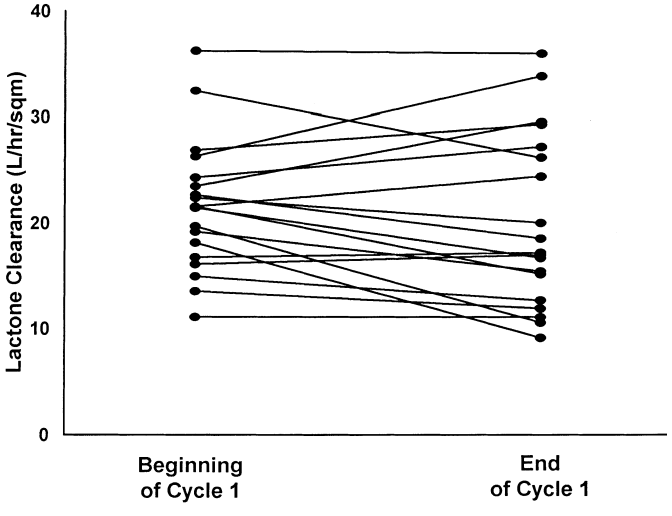

Fig. 3 Topotecan lactone clearance (CL) as determined in children ($n = 19$) at the beginning (days 1, 2) and end {days 20, 21 of the [(d × 21)4] schedule or days 18, 19 of the [(d × 5)3]4 schedule} of cycle 1. *Lines* connect patient-specific CL at the beginning and end of cycle 1

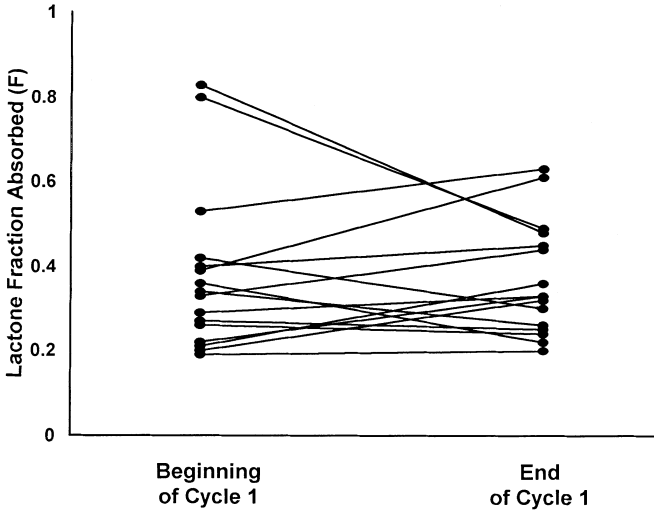

Fig. 4 Topotecan lactone oral fraction absorbed (F) in children ($n = 16$) at the beginning (days 1, 2) and end {days 20, 21 of the [(d × 21)4] schedule or days 18, 19 of the [(d × 5)3]4 schedule} of cycle 1. *Lines* connect patient-specific F at the beginning and end of cycle 1

single oral dose (1.5 mg/m^2) of the i.v. formulation, whereas after doses of 0.8 and 1.1 mg/m^2 in our study the F for topotecan lactone was 0.34 ± 0.15 and 0.33 ± 0.16, respectively.

Interpatient variability in topotecan disposition after oral and i.v. administration was relatively large, whereas intrapatient variability was relatively small. Topotecan lactone CL_{sys} varied 3.9-fold between patients (range 9.2–36.3 l h^{-1} m^{-2}, CV 31.5%), whereas the change within patients over the 3-week treatment period was a median of 1.2-fold (range 1.0- to 1.9-fold, CV 16.7%). The relatively large interpatient and small intrapatient variability in topotecan systemic disposition was consistent with the results of our previous studies [4, 24]. Topotecan lactone clearance has varied from 4.5 to 48.6 l h^{-1} m^{-2} in children with leukemia or solid tumors [4], whereas clearance within patients remains constant within a single course and during subsequent courses [25]. In addition, a significantly greater interpatient versus intrapatient variability was observed in oral absorption of topotecan. The topotecan F varied 6.2-fold between patients (range 0.14–0.72, CV 41.2%), whereas the change within patients was a median of 1.4-fold (range 1.1- to 1.8-fold, CV 15.2%). The clinical relevance of the interpatient variability in topotecan clearance and oral bioavailability is based on the steep topotecan systemic exposure-response relationship we have reported for toxicity and efficacy [4, 14, 15, 24, 26]. Moreover, the interpatient variability reflected in the overlap of topotecan systemic exposures at the 0.8- and 1.1-mg/m^2 doses confounds the use of dose as a measure of topotecan treatment intensity [24, 27–30].

Topotecan is a pentacyclic structure with a lactone moiety in the E ring. In vitro studies have shown that an intact lactone ring is essential for cytotoxicity [31, 32]. The lactone ring undergoes a reversible pH-dependent hydrolysis to form the inactive hydroxy acid form. At an acidic pH the lactone form predominates; however, at physiologic pH the hydroxy acid form predominates [13]. In vitro studies performed in non-protein-containing buffer solutions at a pH of 7.4 report that approximately 30% of topotecan occurs in the lactone form [13], whereas in our clinical studies the percentage of lactone has varied from 20% to 68% [4]. It is well known that changes in plasma pH and serum albumin concentration may affect the percentage of lactone. In this paper we report data suggesting that the lactone-to-total-concentration ratio is consistently greater after oral administration than after i.v. administration during each interval studied. The acidic pH of the gastrointestinal tract may stabilize the lactone ring structure, ultimately leading to greater absorption and, subsequently, to a higher degree of exposure to the active lactone form. However, the ratio of lactone to total concentration was higher from 15 min to 8 h after oral administration. For gastric pH to be the explanation for the increase in lactone exposure after oral administration, topotecan would have to remain in the gastrointestinal tract and undergo delayed absorption or undergo enterohepatic recycling. Prior studies have suggested that topotecan undergoes hepatic metabolism and enterohepatic recycling [33, 34]; however, we did not observe this in our patients. Regardless, oral topotecan may provide a method of administration by which one could achieve a higher bioavailable exposure to the active lactone form.

Preclinical studies suggest that low-dose protracted administration of topotecan achieves a greater antitumor response than does a high-dose shorter schedule of administration [7, 8, 10, 35]. Oral therapy would provide a convenient method of administration for prolonged treatment and may be useful as maintenance therapy for sensitive tumors. In addition, the higher percentage of topotecan lactone occurring after oral as compared with i.v. administration provides a unique rationale for oral topotecan treatment. Although the oral bioavailability observed in our study was similar to that seen in prior studies in adults, we observed a large interpatient variability in oral bioavailability and disposition but a small intrapatient variability. Obviously, the wide interpatient variability observed in the oral bioavailability of a cytotoxic such as topotecan presents patients with potential risks. Thus, it is essential that additional studies of oral topotecan be conducted to define further the interpatient variability in topotecan oral absorption.

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